PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 :
C07D 491/044, A61K 31/40 // (C07D 491/044, 313:00, 209:00)

A1

(11) International Publication Number: **WO 98/54186**

(43) International Publication Date: 3 December 1998 (03.12.98)

(21) International Application Number: PCT/EP98/03022

(22) International Filing Date: 19 May 1998 (19.05.98)

(30) Priority Data:
97201596.0 26 May 1997 (26.05.97) EP
(34) Countries for which the regional or international application was filed: AT et al.

(71) Applicant *(for all designated States except US)*: AKZO NOBEL N.V. [NL/NL]; Velperweg 76, NL–6824 BM Arnhem (NL).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: HEERES, Gerardus, Johannes [NL/NL]; Zevenbergseweg 24, NL–5351 PH Berghem (NL). VAN BAKEL, Franciscus, Hermanus, Antonius, Adreana [NL/NL]; Leeuwerikstraat 44, NL–5402 XD Uden (NL).

(74) Agent: KRAAK, Hajo; P.O. Box 20, NL–5340 BH Oss (NL).

(81) Designated States: AM, AU, BB, BG, BR, CA, CN, CZ, EE, GE, HU, ID, IS, JP, KG, KP, KR, LK, LR, LT, LV, MD, MG, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, TT, UA, US, UZ, VN, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: SALTS OF AROMATIC SULPHONIC ACIDS

(57) Abstract

The invention is a salt of the CNS–depressant trans–5– chloro–2,3,3a,12b–tetrahydro–2– methyl–1H–dibenz[2,3:6,7] oxepino[4,5–c]pyrrole and a salt–forming agent, the latter being an aromatic sulphonic acid. The disclosed salt, preferably the besylate, has favourable properties. Thus it has the required insolubility and crytallinity in order to be suitable for use in depot injection preparations.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	**ES**	Spain	**LS**	Lesotho	**SI**	Slovenia
AM	Armenia	**FI**	Finland	**LT**	Lithuania	**SK**	Slovakia
AT	Austria	**FR**	France	**LU**	Luxembourg	**SN**	Senegal
AU	Australia	**GA**	Gabon	**LV**	Latvia	**SZ**	Swaziland
AZ	Azerbaijan	**GB**	United Kingdom	**MC**	Monaco	**TD**	Chad
BA	Bosnia and Herzegovina	**GE**	Georgia	**MD**	Republic of Moldova	**TG**	Togo
BB	Barbados	**GH**	Ghana	**MG**	Madagascar	**TJ**	Tajikistan
BE	Belgium	**GN**	Guinea	**MK**	The former Yugoslav Republic of Macedonia	**TM**	Turkmenistan
BF	Burkina Faso	**GR**	Greece			**TR**	Turkey
BG	Bulgaria	**HU**	Hungary	**ML**	Mali	**TT**	Trinidad and Tobago
BJ	Benin	**IE**	Ireland	**MN**	Mongolia	**UA**	Ukraine
BR	Brazil	**IL**	Israel	**MR**	Mauritania	**UG**	Uganda
BY	Belarus	**IS**	Iceland	**MW**	Malawi	**US**	United States of America
CA	Canada	**IT**	Italy	**MX**	Mexico	**UZ**	Uzbekistan
CF	Central African Republic	**JP**	Japan	**NE**	Niger	**VN**	Viet Nam
CG	Congo	**KE**	Kenya	**NL**	Netherlands	**YU**	Yugoslavia
CH	Switzerland	**KG**	Kyrgyzstan	**NO**	Norway	**ZW**	Zimbabwe
CI	Côte d'Ivoire	**KP**	Democratic People's Republic of Korea	**NZ**	New Zealand		
CM	Cameroon			**PL**	Poland		
CN	China	**KR**	Republic of Korea	**PT**	Portugal		
CU	Cuba	**KZ**	Kazakstan	**RO**	Romania		
CZ	Czech Republic	**LC**	Saint Lucia	**RU**	Russian Federation		
DE	Germany	**LI**	Liechtenstein	**SD**	Sudan		
DK	Denmark	**LK**	Sri Lanka	**SE**	Sweden		
EE	Estonia	**LR**	Liberia	**SG**	Singapore		

SALTS OF AROMATIC SULPHONIC ACIDS

The invention pertains to a salt of the compound trans-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole and a salt forming agent.

Such salts are known. Thus, e.g., the maleate of the above compound (Org 5222), as well as the preparation thereof, has been described in US 4,145,434, the disclosure of which is incorporated herein by reference.

The compound is described as having CNS-depressant activity and antihistamine and antiserotonin activities.

The pharmacological profile of trans-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole, its kinetics and metabolism, as well as the first safety and efficacy studies in human volunteers and in schizophrenic patients were reviewed by De Boer et al. (Drugs of the Future 1993, 18(12), 1117-1123). It has been established that Org 5222, which is trans-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole(Z)-2-butenedioate (1:1), is a very potent dopamine and serotonin antagonist and antihistaminic with potential antipsychotic activity.

In view of the compound's utility, it is desired for it to be incorporated into pharmaceutical compositions of all kind and, notably, those that are advantageous with regard to administering to patients suffering from mental disorders. Due to the vary nature of their disease, these patients frequently refuse to take their medicine or simply forget to take it, e.g. as a result of apathy. In view hereof, it is highly desired for compounds such as the above, to be administered in the form of a depot preparation, i.e. a pharmaceutical composition containing a dose of the medicine sufficient for a prolonged time, e.g. several weeks, and which by means of sustained release will perform its desired function to the central nervous system.

The known compounds, however, are not very well suitable for use in such depot preparations. The main requirements for such a use are that the compound is crystalline (otherwise the compound will be metastable, due to which it cannot be predicted what, at a certain point in time, the amount of biologically desired compound is) and that it has a low solubility in water. The latter is important for attaining the required sustained release. E.g. the maleate, (the (Z)-2-butenedioate Org 5222), which is crystalline, has a solubility of 3 mg/ml (21°C) which means that also higher doses, intended for controlled sustained release, will be taken up in the patient's blood immediately. The free base (Org 33254) has a relatively low solubility of less then 0.1 mg/ml, but is instable. The pamoate (Org 33388) is amorphous, the hemipamoate (Org 39058) is a mixture of amorphous and crystalline material. Further, it is desired that the melting point is not too low (preferably above 80°C), as this may lead to temperature-induced problems when making tablets or granules.

For long it has been recognized in the art that there is no reliable way of predicting the influence of a particular salt species on the behaviour of the parent compound, see e.g. J.Pharm.Sci. 66, 1-19, 1977. Salt-forming agents are therefore generally chosen empirically, and also in later literature, e.g. International Journal of Pharmaceutics, 33 (1986) 201-217, it has been recognized that, notably for properties such as hygroscopicity, stability and solubility, it is difficult to select the salt forming agent beforehand.

The same holds for the present compounds, all the more since also crystallinity is required. Hence it is an object of the present invention to select a salt-forming agent for the above compound which leads to this pharmacon being substantially water-insoluble, and crystalline.

According to the invention the salt-forming agent selected is an aromatic sulphonic acid.

Although in principle any pharmaceutically acceptable aromatic sulphonic acid is suitable, some aromatic moieties are clearly preferred. Thus the aromatic moiety may advantageously be of the type having a single phenyl ring. Preferred acids of this type being benzene sulphonic acid and toluene sulphonic acid, the preferred salts of the invention are the besylate and the tosylate. In the alternative, it may be advantageous for

the aromatic moiety to be unsubstituted (apart from the sulphonic acid group of course). In this respect not only the besylate is the preferred salt of the invention, but naphthalene sulphonic acid is also a suitable candidate for the acid, resulting in the corresponding napsylate. However, the most preferred salt of the invention is the besylate.

The salts of the present invention can be prepared analogously to those described in US 4,145,434. For the preparation of the compound trans-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole reference is made to said document. In order to obtain the desired salt, said compound can be dissolved in a suitable solvent, such as ethanol and then be mixed with a solution of the appropriate aromatic sulphonic acid, preferably in the same solvent or in a solvent miscible with the solvent for said compound. The mixture then can be allowed to stand for sufficient time to let the corresponding salt according to the invention crystallize (which occurs spontaneously). If desired the obtained crystals can further undergo conventional washing and drying and/or purifying steps, e.g. simple recrystallization followed by drying.

Just as the known maleates, the compositions of the invention are useful in treating mammals, including humans, suffering from all diseases susceptible to treatment by trans-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole. These diseases include mental disorders, such as tension, excitation, anxiety, psychosis, and schizophrenia. The compositions may also be used for antidopamine, antihistamine and for antiserotonin related diseases.

Hence, the salts of the present invention have a utility as a medicine *per se*, and they may be administered in any form, although, as described in WO 95/23600, peroral administration may lead to cardiotoxic side-effects. Thus other forms of administration are preferred, e.g. subcutaneous administration, injection, or by means of sublingual or buccal pharmaceutical composition as described in WO 95/23600.

All of these single dosage forms of pharmaceutical compositions containing the salt of the present invention comprise one dosage unit of trans-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole as an active ingredient. A dosage unit may contain between 0.005 mg and 15 mg of the active ingredient. Preferably the dosage

unit contains of from about 0.03 to 0.50 mg of trans-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole. Any suitable, pharmaceutically acceptable carrier material may be applied, and pharmaceutically acceptable auxiliaries be added. All of these pharmaceutically acceptable excipients such as carriers and auxiliaries are known to the person skilled in the art and do not require elucidation here.

It is preferred, and only possible as a result of the present invention, that the salt be administered by means of a depot injection, i.e. at a dose higher than that in a single dosage form. Typical doses for such preparations comprise 10 to 40 mg of the active ingredient. The depot preparations of the present invention in its simplest form may comprise water as a carrier, the low aqueous solubility of the salt of course making it preferable for it to be dispersed rather than dissolved. To facilitate making a stable dispersion, conventional adjuvants may be used, e.g. Tween (surfactant), propylene glycol, lecithin, etc. Other pharmaceutically acceptable carriers are also suitable, e.g. carboxy methyl cellulose, gelatin, poly(vinyl pyrrolidone), or other well-known excipients. For background knowledge of depot preparations reference is made to Leiberman, Rieger, Bunker, Pharmaceutical Dosage Forms: Disperse System, Volume 2.

The invention is further illustrated with reference to the following examples.

EXAMPLE I

A solution of 940 mg of benzene sulphonic acid in 15 ml of ethanol was added to a solution of 1.7 g of trans-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz[2,3:6,7]-oxepino[4,5-c]pyrrole. Crystallization occurred, and the crystals obtained were collected and recrystallized from 75 ml of boiling ethanol. After cooling to 20°C the crystals were collected and dried *in vacuo* over calcium chloride and potassium hydroxide. Yield: 1.9 g (72%) of trans-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole benzene sulphonate (besylate). This salt was found to have a melting point of 227.8°C and a solubility in water measured at 20°C of $<<1$ mg/ml.

COMPARATIVE EXAMPLE

The procedure of Example 1 was repeated, employing a great many different acids, all known for their suitability as a salt-forming agent for a pharmacon. The results attained are given in the following table:

TABLE

Salt	**Form**	**Melting point (°C)**	**Solubility in water (mg/ml)**
maleate	crystalline	141-145	3
fumarate	crystalline	185.5-187	1
1-hydroxy naphthoate	no crystallization	-	-
palmitate	no crystallization	-	-
pamoate	amorphous	230-240	<0.35
hemipamoate	amorphous /crystalline	167-168	<0.25
benzoate	no crystallization	-	-
2-hydroxy benzoate	no crystallization	-	-
4-acetyl amino benzoate	no crystallization	-	-
3-hydroxy-2-naphthoate	no crystallization	-	-
2-methoxy phenyl acetate	no crystallization	-	-

Clearly, the aromatic sulphonates of the invention form an exception in combining the desired properties of being crystalline, having a high melting point and displaying such a low solubility in water as to be held water-insoluble.

EXAMPLE II

The procedure of Example I was repeated, substituting toluene-4-sulphonic acid for benzene sulphonic acid. Thus the corresponding toluene sulphonate (tosylate) was obtained.

EXAMPLE III

The procedure of Example I was repeated, substituting naphthalene-1-sulphonic acid and naphthalene-2-sulphonic acid for benzene sulphonic acid. Thus the corresponding naphthalene sulphonates (napsylates) were obtained.

Claims:

1. A salt of trans-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz[2,3:6,7]oxepino-[4,5-c]pyrrole and a salt forming agent, characterized in that the salt forming agent is an aromatic sulphonic acid.

2. A salt according to claim 1, characterized in that the aromatic moiety of the aromatic sulphonic acid is a single phenyl ring.

3. A salt according to claim 2, characterized by being the tosylate or besylate.

4. A salt according to claim 1, characterized in that the aromatic moiety of the aromatic sulphonic acid is unsubstituted.

5. A salt according to claim 4, characterized by being the napsylate or besylate.

6. The aromatic sulphonate of trans-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole as a medicine.

7. Trans-5-chloro-2-methyl-2,3,3a,12b-tetrahydro-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole besylate as a medicine.

8. A pharmaceutical composition comprising a salt of trans-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole as a medicinally active compound and a pharmaceutically acceptable carrier, characterized in that the salt is an aromatic sulphonate.

9. A pharmaceutical composition according to claim 8, characterized in that the aromatic sulphonate is selected from the group consisting of tosylate, besylate, napsylate, and mixtures thereof.

10. A depot injection preparation comprising an aromatic sulphonate of trans-5-chloro-2,3,3a,12b-tetrahydro-2-methyl-1H-dibenz[2,3:6,7]oxepino[4,5-c]pyrrole and a pharmaceutically acceptable carrier suitable for use in depot injection preparations.

5

INTERNATIONAL SEARCH REPORT

Inte. .onal Application No
PCT/EP 98/03022

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D491/044 A61K31/40 //(C07D491/044,313:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 145 434 A (VAN DER BURG) 20 March 1979 cited in the application see column 9, line 22 - line 27; claims 1,21	1,8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
14 September 1998	22/09/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Alfaro Faus, I

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte. ..onal Application No
PCT/EP 98/03022

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4145434 A	20-03-1979	NL 7605526 A	28-11-1977
		AU 509073 B	17-04-1980
		AU 2533177 A	23-11-1978
		BE 854915 A	23-11-1977
		CA 1122976 A	04-05-1982
		CH 637382 A	29-07-1983
		CH 633536 A	15-12-1982
		DE 2723209 A	15-12-1977
		DE 2760372 C	29-05-1991
		DK 227477 A,B,	25-11-1977
		FI 771635 A,B,	25-11-1977
		FI 832085 A,B,	09-06-1983
		FR 2352800 A	23-12-1977
		GB 1567862 A	21-05-1980
		JP 1432301 C	24-03-1988
		JP 61178965 A	11-08-1986
		JP 62038348 B	17-08-1987
		JP 1367795 C	11-03-1987
		JP 53002465 A	11-01-1978
		JP 61034426 B	07-08-1986
		LU 77387 A	29-08-1977
		SE 436202 B	19-11-1984
		SE 7705957 A	25-11-1977
		US 4154836 A	15-05-1979
		US 4158059 A	12-06-1979
		US 4177275 A	04-12-1979
		US 4271177 A	02-06-1981
		US 4158058 A	12-06-1979
		US 4271178 A	02-06-1981
		US 4271179 A	02-06-1981
		ZA 7702752 A	26-04-1978